DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service 5 4 4 0 8 d

Food and Drug Administration
Detroit District
300 River Place
Suite 5900
Detroit, MI 48207
Telephone: 313-393-8100
FAX: 313-393-8139

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

WARNING LETTER
2004 - DT- 02

November 19, 2003

Anthony J. Moravec
President and CEO
Applied Laboratories, Inc.
3240 N. Indianapolis Road
Columbus, IN 47201

Dear Mr. Moravec:

An inspection was conducted of your medical device and drug manufacturing operations on September 16-30, 2003. The inspection revealed that, among other things, your firm manufactures a solution for the care of contact lenses (Sterile Saline Solution for Care and Storage of Contact Lenses) that is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act)(see also Title 21, Code of Federal Regulations (CFR), section 886.5928).

Our inspection found that your firm is operating in violation of the Quality System Regulation (QSR), 21, CFR Part 820, rendering your devices adulterated within the meaning of section 501(h) of the Act in that the methods used in, or the facilities or controls used for, manufacturing, packing, storage, or installation are not in compliance with the QSR. The FORM FDA-483, List of Inspectional Observations, issued to you at the conclusion of FDA's inspection (copy enclosed) describes, among others, the following deviations from the QSR:

1. You failed to appoint a manager with executive responsibility to be the "Management Representative" (FDA-483 # 2) as required by 21 CFR 820.20(b) (3).

2. You failed to conduct management review of the suitability and effectiveness of the quality system (FDA-483 # 3) as required by 21 CFR 820.20(c).

3. You failed to conduct internal quality audits in 2002 (FDA-483 # 7) as required by 21 CFR 820.22 and by your procedure #011-SOP2170.00-01 effective 12/28/00.

4. You failed to have written procedures for handling Medical Device Reporting (FDA-483 # 11) as required by 21 CFR 803.17.

5. Your complaint handling procedure, #002-SOP1008.00 effective 12/10/99 failed to include steps to ensure complaints are evaluated to determine whether they represent an event which is required to be reported to FDA under the Medical Device Reporting regulation, (FDA-483 #12) as required by 21 CFR 820.198(a)(3).

6. Your Corrective and Preventive Action procedure #2149.00 effective 6/4/99 was found to lack provisions for review of all appropriate systems, verification or validation of the corrections, and submitting the relevant information for management review, (FDA-483 #13) as required by 21 CFR 820.100(a)(1).

7. Your change control procedure #011-SOP2180.00 effective 7/14/03 was found to lack provisions for complete documentation of the nature and approval of production and process changes, (FDA-483 #14) as required by 21 CFR 820.70(b). Specifically, the review and approval process for each of the ten changes to the Master Batch Record for 12 oz Equate Buffered Saline, revision # 09 effective 08.06.02 were not documented.

8. You failed to perform process validation of the filling and crimping process, (FDA-483 #16) as required by 21 CFR 820.75(a).

The above is not intended to be an all-inclusive list of deficiencies at your firm. There were other inspectional observations listed on the FDA-483 not included in the above list of violations that require your attention. It is your responsibility to assure adherence to each requirement of the Quality System Regulation. Other Federal agencies are advised of the issuance of all Warning Letters about medical devices so they may take this information into account when considering the award of contracts. Additionally, no pre-market submissions for devices to which the QSR deficiencies are reasonably related and no Certificates of Exportability will be approved until the above violations are corrected.

We request that you take prompt action to correct these violations and to ensure that your device manufacturing operations are in full compliance with the Act and regulations promulgated thereunder. Failure to promptly correct these violations may result in enforcement action being initiated by the Food and Drug Administration without further notice, such as seizure and/or injunction.

We acknowledge receipt of the October 23, 2003 letter from Ms. K. Nicole Harter, Director of Quality Assurance, directed to Joann Givens, District Director, in response to the FDA-483. The actions described in that letter indicate your firm is in the process of correcting the specific observations listed on the FDA-483. We have the following comments regarding certain of those corrective actions.

FDA-483 #2 Management Representative
A memo of 9/29/03 designates Mr. Moravec to be Head of the Management Review Team, and Procedure No. 002-SOP0204.00, Revision No. 03, was amended to define the Management Representative to be the Head of the Management Review Team. The changes in the revised procedure do not include an outline of the specific duties to be handled by the Management Representative/Head of the Management Review Team. The procedure also references two CFR regulations that are **NOT** correct for either the Management Representative, 21 CFR 820.20(b)(3), or for the drug Annual Product Review, 21 CFR 211.180(e).

Our November 2000 inspection of your firm reported [redacted], Director of Regulatory Affairs to be the Management Representative. Our September 1998 inspection reported [redacted] to be Vice President of Regulatory Affairs although the assignment of Management Representative was not determined. Our latest inspection found the position of Director of Regulatory Affairs to be vacant, and the Management Representative designation to be undefined and unfilled. We are concerned that the inconsistent assignment and performance of the Management Representative duties is related to the problems identified during the recent inspection. We recommend you carefully review the requirements of the Quality System Regulation, 21 CFR 820 with special attention to Subpart B concerning Management, Audits, and Personnel. Although the assignment of the Management Representative functions to Mr. Anthony Moravec will surely elevate their visibility, we suggest you consider the assignment to an individual who can focus more time and attention to this specialized area.

FDA-483 #14 Production and Process Change Controls
We accept your revised procedure #011-SOP2180.00, Revision 02, effective 10/20/03, Section 2.6, that provides for an evaluation of process changes to determine if validation of the procedure is necessary.

The documents supporting FDA-483 #14 were further reviewed after the inspection and an inconsistency was noted concerning the Deviation Report # D-A0311, and the indicated change made to the 12 oz Equate Master Batch Record, Revision #9, dated 08.06.02. The FDA Investigator wrote in his inspection report that he was told Deviation D-A0311 relates to item #4 on the list of revisions. Item #4 concerns the added step, [redacted]" Deviation D-A0311 concerns changing the frequency of QC Inspection checks from [redacted], None of the ten items listed as changed refer to the frequency of QC checks.

FDA-483 #16 Process Validation
We acknowledge your new Process Validation Protocol # VAL9007P-00 effective Oct 21, 2003, designed to validate the total manufacturing process for 12 oz Buffered Saline. The principle step in this process needing validation is the FILLING/PACKAGING PROCEDURE step #2 on page 5 of the Master Batch Record. Validation of this step is necessary because the measurable specifications cannot be verified without destructive testing of every unit. Section 6.2, Equipment Qualifications states the aerosol filler Installation and Operational Qualifications are on file however there is no mention of such installation and operational data for the crimper/charger machine. Section 6.3.2, the Packaging Process phase of the protocol does not establish criteria for evaluation of the integrity of the finished container closure to assure a robust barrier to maintain sterility of the product. Section 7.0, Sampling Methods, Table 2, does not explain the rationale for determining the sample size for pressure and extrusion (volume) testing, and lacks any testing for crimp radial, crimp depth and gasket compression measurements that are performed in your routine QC checks.

FDA-483 # 19 Drugs - Cleaning Validation
We acknowledge your updated protocol VAL926700C-00 effective 10/23/03 for the validation of equipment cleaning following production of [redacted] and encourage you to complete this long delayed study as quickly as your production schedule of [redacted] allows. The FDA Investigator stated in his report he was informed this cleaning validation protocol was initially prepared in April 2000 but never implemented pending an agreement with the contracting customer. The requirement for validation of equipment cleaning procedures, 21 CFR 211.67, serves to protect your other drug and medical device products from the potential adverse effects of the [redacted] if cross contamination were to occur.

It is your responsibility to assure your cleaning procedures are validated, and this should not have been left up to an agreement by the customer.

We have reviewed the [redacted] cleaning validation protocol and noted there is no indication that recovery studies were performed with the Total Organic Carbon analytical test using samples spiked with the [redacted] product as well as samples spiked with the cleaning compounds. The validation also provides no rational for testing only rinse water samples, instead of contact swab sampling. Enclosed for your consideration is a copy of the FDA Guide to inspections validation of cleaning procedures.

The responses to the remaining observations listed on the FDA-483 appear to be satisfactory, and will be evaluated during our next inspection.

Please notify this office in writing, within fifteen (15) working days of your receipt of this letter, of any steps you have taken, or intend to take, regarding the deviations from the QSR noted in items 1 through 8 on the first two pages of this letter, to bring your firm into compliance. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the time frame within which the corrections will be implemented.

Your response should be directed to Melvin O. Robinson, Compliance Officer, at the above address.

Sincerely yours,

David M. Kaszubski
for Joann M. Givens
Director, Detroit District

Enclosures
FDA-483
Guide to inspections validation of cleaning procedures